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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,426	07/02/2001	Kazutoshi Watanabe	P20810	7478

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,426	WATANABE ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28,30-33 and 35-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,30-33 and 35-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of 4-22-05 has been fully considered. Although applicant's argument has overcome the previous 103 rejection based solely on **Skulnick et. al.**, a review of prior arts of record shows that pending claims can still be obvious over **Skulnick et. al.** in view of **Spohr et. al.** (US'753 – cited previously). Furthermore, an update search yields a new reference which can also render obvious claim 42. Therefore, new grounds of rejection are presented herein.

Claims 1-26, 29 and 34 have been cancelled.

Claims 27, 28, 30-33 and 35-42 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement:** Claim 42 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of Alzheimer's disease with a compound of formula (I) wherein R^5 *is a optional substituted phenyl group (or* C_6 *aryl group)*, does not reasonably provide enablement for the treatment of Alzheimer's disease with a compound of formula (I) wherein R^5 *is a hydrogen or optional substituted alkyl, alkenyl, alkynyl or cylcoalkyl group*. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 42 recites: "A method for therapeutic treatment of Alzheimer disease, which comprises administering to a patient a therapeutically effective amount of a substance selected from the group consisting of a pyrimidone compound represented by formula (I)....R^1 represents a group represented by $-N(R^4)-W-R^5$....R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group..., a C_3-C_{18} alkenyl group..., C_3-C_{18} alkynyl group..., a C_3-C_8 cycloalkyl group..., or a C_6-C_{14} aryl group..." Thus, the scope of formula (I) in claim 42 covers a large number of compounds.

The amount of direction or guidance presented: On pages 92-95, the specification describes an *in-vitro* assay showing several compounds with inhibitory activity on bovine

cerebral TPK1. However, there is no *in-vivo* assay to show if the claimed compounds can increase memory, or inhibit neurodegeneration. The inhibition of TPK1 only suppresses the Aβ neurotoxicity, which is not conclusive on halting neurons from degeneration. Thus, the specification does not provide sufficient guidance on treating Alzheimer's disease using an array of compounds of formula (I).

The state of the prior art: The teaching of **Aldrich et. al.** (US 6,107,301) discloses a class of substituted (2-phenylamino)-pyrimidyl compounds that can inhibit CRF receptor and treat a number of neurological diseases such as: depression, anxiety, or Alzheimer's. Thus, it would be reasonable to expect a compound of the instant formula (I) wherein R^1 is –NH-R^5 with R^5 as a phenyl group to have CRF activity which could treat Alzheimer's disease.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to engage in undue experimentation to establish data that would adequately support the use of the claimed compounds in the treatment Alzheimer's disease. Such a task would require a tremendous amount of effort, time and resources.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only shows *in-vitro* data for the inhibition of bovine cerebral TPK 1. However, said evidence does not adequately guide the skilled clinician in the treatment of Alzheimer's disease. With the teaching of Aldrich et. al., the skilled clinician could select a few compounds of the instant formula (I) for such a treatment. Thus, with such a limited

teaching, the skilled clinician would have to carry out undue experimentation to use compounds of formula (I) that are not analogous to those of Aldrich et. al. in the methods recited in claim 42.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 27, 28, 30-33 and 35-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Skulnick et. al.** (J. Med. Chem. – cited previously) and further in view of **Spohr et. al.** (US 6,096,753). On page 1867, Skunick et. al. disclose two pyrimidinone compounds (#112 & #113) that are homologous to the compounds of the instantly claimed formula (I) with the following substituents:

i. R^2 is hydrogen or halogen atom;

ii. R^3 is 4-pyridyl;

iii. R^1 is $-N(R^4)-W-R^5$;

iv. With W as a single bond and R^4 as hydrogen, R^1 is reduced to $-NHR^5$.

The disclosed compounds differ from those claimed herein by having $-NH_2$ (or a primary amine) at the second position of the pyrimidine ring, and not $-NHR^5$ (or a secondary amine).

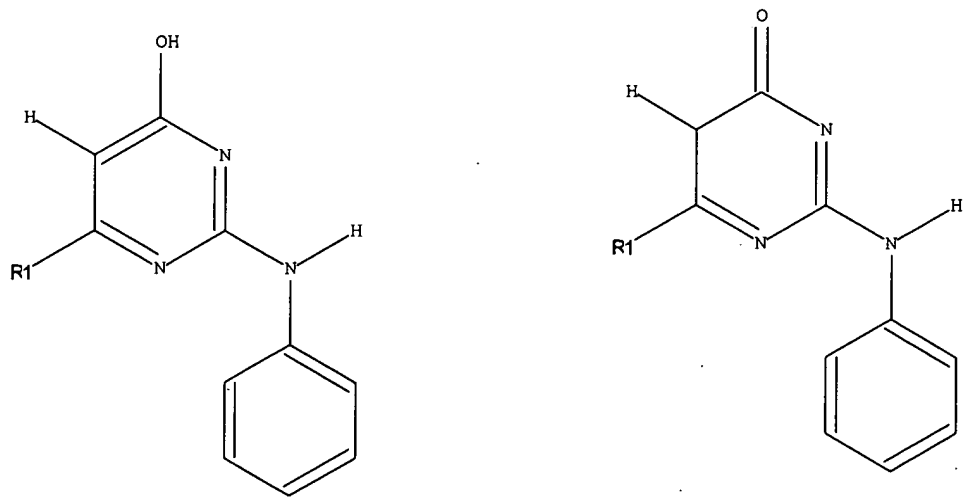
Applicant argued that Skunick et. al. do not provide motivation for modifying the second position of the pyrimidine ring. That is, Skunick et. al. do not provide motivation for replacing $-NH_2$ with a secondary amine equivalent to $-NHR^5$ to maintain the same antiviral activity.

However, such a difference can be overcome by the teaching of **Spohr et. al.** On columns 4-14, Spohr et. al. disclose a genus of pyrimidone compounds represented by formula (I). In said formula, the pyrimidone ring is substituted at the second position with a group represented by R, which can be R_1. Variable R_1 represents Y which can be $-NR_5R_{21}$ (see column 9, line 43). The disclosed R_5 can be *hydrogen, alkyl, alkenyl, alkynyl, aryl, etc.* (see column 9, lines 30-36), and R_{21} can be *hydrogen, alkyl, aryl, etc.* (see column 14, line 42). Thus, the generic teaching of **Spohr et. al.** provides equivalent teaching for a primary amine (or $-NH_2$) and a secondary amine such as $-NHR^5$.

Because Spohr's compounds can also treat viral infection (see column 1, lines 38-40), with the equivalent teaching provided, the skilled medicinal chemist would have been motivated to modify Skulnick's compounds by replacing the $-NH_2$ with a secondary amine group to obtain compound of the instantly claimed formula (I) wherein R^1 is $-NHR^5$.

Thus, at the time that the invention was made it would have been obvious to make compounds claimed herein and use them as antiviral agents in view of the combined teachings above.

3. Claims 27, 28, 30-33 and 35-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Aldrich et. al.** (US 6,107,301). On column 36, Aldrich et. al. disclose formula (XVI) which is a tautomer of formula (I) claimed herein. See the following structures:



(XVI)

The disclosed formula is a tautomer of formula (I) with the following substituents:

- R^2 is hydrogen;
- R^1 is $-N(R^4)-W-R^5$;
- With W as a single bond and R^4 as hydrogen, R^1 is reduced to $-NHR^5$;
- R^5 is an aryl group which maybe substituted.

Note, the definition of R^1-R^3 in US'301 allows for substituents that can form a tautomer.

That is, when the reference's R^2 is hydrogen, and its R^3 is $-OR^8$ (wherein R^8 is hydrogen and thus, R^3 is –OH), then formula (XVI) is a tautomer of formula I claimed herein. The disclosed R^1 can be NR^6R^7 – with R^6 and R^7 forming a ring, R^1 is equivalent to the instant R^3.

Although formula (XVI) is shown as an intermediate, the disclosed formula (I) includes compounds of formula (XVI) as final products as well. Because said compounds can treat Alzheimer's disease, the skilled medicinal chemist would have been motivated to make compounds of the instant formula (I) from the disclosed tautomer of formula (XVI) since tautomers exist in equilibrium and share the same biological property.

Thus, at the time of the invention, it would have been obvious to make and use compounds as claimed herein in view of the teaching above.

No pending claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Tamthom N. Truong
Examiner
Art Unit 1624

7-10-05

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